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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/756,690 | 01/09/2001 | Orville G. Kolterman | 030639.0066.UTL | 4666 |

7590 04/10/2003

ARNOLD AND PORTER
IP DOCKETING DEPARTMENT, ROOM 1126B
555 TWELFTH STREET, NW
WASHINGTON, DC 20004-1206

| EXAMINER | |
|---|---|
| JIANG, DONG | |
| ART UNIT | PAPER NUMBER |
| 1646 | |

DATE MAILED: 04/10/2003

25

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/756,690 | Applicant(s) KOLTERMAN ET AL. | |
|---|---|---|---|
| | Examiner Dong Jiang | Art Unit 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *16-18,21-23 and 38-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,19,20,24-37 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-40* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,16,19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

**DETAILED OFFICE ACTION**

Applicant's species election with traverse of exendin-4 in Paper No. 21, filed on 23 January 2003 is acknowledged. The traversal is on the ground(s) of the close relationship and common utility of the various species, and that there are only nice species, and examination of the entire application can be made without a serious burden. This argument is persuasive with respect to the six specified exendin-4 agonists in claims 13, 35 and 41, and requirement for the species restriction among the six exendin-4 agonists is withdrawn. This argument is not found persuasive with respect to the three formulas in claims 16-18, 21-23 and 38-40 because the majority of the amino acid residues in all three formulas are "Xaa"s, and each Xaa is assigned with multiple different possibilities of amino acids, which in total constitute thousands of possible polypeptide sequences. Each potential polypeptide, by itself, is a patentably distinct invention, and each represents a unique and separately patentable sequence, because each has the unique sequence structure, thus requires separate searches of the prior art. Searching all of the sequences in a single patent application would constitute an undue search burden on the examiner and the USPTO's resources because of the non-coextensive nature of these searches.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's amendment in Paper No. 21, filed on 23 January 2003 is acknowledged and entered. Following the amendment, the new claim 41 is added.

Currently, claims 1-41 are pending, and claims 1-15, 19, 20, 24-37 and 41 are under consideration. Accordingly, claims 16-18, 21-23 and 38-40, as non-elected inventions, are withdrawn from consideration.

***Formal Matters:***

***Priority***

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This

should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a0 on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

***Objections and Rejections under 35 U.S.C. 112:***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7, 14, 28-30 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is indefinite for reciting "about 1 ug-30 ug to about 1 mg". As all of dosages between 1-30 ug and 1 mg are embraced by 1 ug to 1 mg, it is unclear why "-30 ug" is needed since the lowest dosage (1 ug) is the only pertinent limitation. Claims 6, 7, and 28-30 are similarly indefinite.

Claim 14 is indefinite because it is unclear what "an exendin *analog or derivative*" refers to, and the specification does not define such. The metes and bounds of the claim, therefore, cannot be determined. Claim 36 is similarly indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 24-37 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method for lowering or reducing triglyceride levels, does not reasonably provide enablement for claims to a method for *modulating* triglyceride levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claims 1-15, 24-37 and 41 are directed to a method for modulating triglyceride levels. The claim limitation of "modulating" in claims 1, 10, and 24 reads on both increasing and

reducing. As only the compounds with one type of action (*agonists* of exendin, or exendins) are used in the claimed method, it can only be effective in one way, either increasing or reducing, but not both. As the specification teaches that exendins and exendin agonists are useful in lowering plasma triglyceride concentration in subjects with elevated triglyceride levels (page 15, the second paragraph from the last), and the prior art indicates that exendins and exendin agonists can lower plasma lipids (see under "*Rejections Over Prior Art*" below), administration of an exendin or exendin agonist would only result reducing plasma triglyceride levels. Additionally, the specification provides no guidance or working examples indicating otherwise (the "increasing" effect). Therefore, while the claimed methods are enabled for lowering triglyceride levels, it is not enabled for increasing thereof.

Due to the lack of direction/guidance presented in the specification regarding "increasing" effect of exendins and exendin agonists in the claimed conditions, the absence of working examples directed to same, the art indicating the increasing effect of exendins and exendin agonists on plasma triglyceride levels, and the breadth of the claims which embrace both increasing and reducing effect of exendins and exendin agonists, the specification does not enable any person skilled in the art to use the claimed invention in its full scope.

***Rejections Over Prior Art:***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 6, 9-14, 19, 20, 24, 26, 28, 29, 32-36 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Beeley et al., WO 98/30231 (provided by applicants), and as evidenced by Beers et al. (the Merck Manual, 17$^{th}$ edition, page 200).

Beeley discloses a method for lowering plasma lipids in a subject including human comprising administering a therapeutically effective amount of an exendin or an exendin agonist (page 10, lines 12-15, and claims 15-18 and 27), wherein the exendin is exendin-3 or exendin-4, and the exendin agonists include exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28)

amide, $^{14}$Leu, $^{25}$Phe exendin-4 amide, and $^{14}$Leu, $^{25}$Phe exendin-4 (1-28) amide (page 10, line 19 to page 11, line 11). Even though Beeley does not specifically mention the term "triglyceride" (as in claim 1), it is well established in the art, and evidenced by Beers that the triglycerides are *major* plasma lipids, which also include cholesterol. As such, Beeley's method for lowering plasma lipids would inherently lower the triglyceride levels. With respect to the limitation of treating "dyslipidemia" in claim 19, Beeley's method for lowering plasma lipids is treating a type of dyslipidemia. With respect to the limitation of modulating "postprandial triglyceride levels" in claim 24, as the method steps of the claim are the same as those of Beeley's method, Beeley's method would inherently modulate postprandial triglyceride levels. Therefore, the reference anticipates claims 1, 9, 11-14, 19, 20, 24, 32-36 and 41. Additionally, Beeley teaches that said method may also be used to reduce the cardiac risk (page 10, lines 16-19), that the exendin or the exendin agonist is administered preferably by injection, that the dose for the administration can be about 10-30 ug to about 1 mg, or about 30 ug to about 500 ug per day (page 9, line 28 to page 10, line 3). Thus, the reference anticipates claims 3, 5, 6, 10, 26, 28 and 29.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, 7, 8, 25, 27, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beeley et al., WO 98/30231, as applied to claims 1, 3, 5, 6, 9-14, 19, 20, 24, 26, 28, 29, 32-36 and 41 above.

The teachings of Beeley are reviewed above. Beeley does not specify the continuous administration (as claims 2 and 25) or a subcutaneous injection (as claims 4 and 27), nor a dose range of about 1-30 ug to about 100 ug, or about 3 ug to about 50 ug per day (as claims 7, 8, 30 and 31). However, given the current state of the art, determination of an appropriate way of administering a drug, and its applicable dose range is well within the purview of a person of ordinary skill in the art, and therefore, "administered continuously", "a subcutaneous injection", and said dose ranges are considered prima facie obvious in the absence of any unexpected result.

Claims 15 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beeley et al., WO 98/30231, as applied to claims 1, 3, 5, 6, 9-14, 19, 20, 41 above, and further in view of Wagle et al., US 6,326,396 B1.

The teachings of Beeley are reviewed above. Beeley does not teach to use an exendin or an exendin agonist in combination with a statin.

Wagle teaches that HMG-CoA reductase inhibitors (also known as "statins") are agents acting directly on plasma triglyceride and cholesterol content, and are effective in lowering triglyceride and cholesterol content, and that lowering of circulating lipids has been to reduce the cardiovascular morbidity (column 2, lines 28-33).

It would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the references and to combine an exendin or an exendin agonist with a statin (HMG-CoA reductase inhibitor) for lowering plasma lipid levels because each of the two drugs is well known for its effect on lowering plasma lipid. The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art of methods using exendins or exendin agonists, or statins for treating

diabetes, it would have been obvious to combine the two drugs for lowering plasma triglyceride and cholesterol because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful for the same purpose of lowering plasma lipid. Thus, claims that require no more than adding together of two conventional drugs set forth prima facie obvious subject matter. The person of ordinary skill in the art would have been motivated to do so because Wagle teaches that lowering plasma triglyceride and cholesterol is beneficial for reducing the cardiovascular morbidity, and reasonably would have expected success because both drugs had been demonstrated in the prior art to be effective on lowering plasma lipid.

***Conclusion:***

No claim is allowed.

***Advisory Information:***

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
3/25/03